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A Phase IIb Dose-Ranging Randomised Study of Efficacy, Patient-Reported Outcomes and Safety of the Anti-Granulocyte Macrophage Colony-Stimulating Factor Antibody Otilimab (GSK3196165) in Patients with Rheumatoid Arthritis

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SUMMARY (497 words)

Background The human monoclonal antibody otilimab inhibits granulocyte-macrophage colony-stimulating factor (GM-CSF), a key driver in immune-mediated inflammatory conditions. We evaluated the efficacy, safety, and key patient-reported outcomes related to pain of otilimab in patients with active rheumatoid arthritis (RA).

Methods This Phase IIb, dose-ranging, multicentre, placebo-controlled study was conducted at 64 sites across 14 countries. Patients aged ≥18 years with RA and receiving stable methotrexate were randomised (1:1:1:1:1:1) to subcutaneous placebo or otilimab 22·5, 45, 90, 135 or 180 mg, plus methotrexate, once weekly for 5 weeks, then every other week until week 50. The randomisation schedule was generated by the sponsor and patients assigned to treatment via interactive response technology. Randomisation was blocked (block size of six) but was not stratified. Investigators, patients, and the sponsor were blinded to treatment. An unblinded administrator prepared and administered the study drug. The primary endpoint was DAS28(CRP) <2·6 at week 24. Patients not in the otilimab 180 mg group, without a good/moderate European League Against Rheumatism response (week 12) or with disease activity score for 28 joints with C-reactive protein (DAS28[CRP]) >3·2 (week 24) escaped to otilimab 180 mg; those who escaped were treated as non-responders in their original randomised group. Safety endpoints were incidence of adverse events (AEs) and serious AEs (SAEs), infections and pulmonary events. Efficacy and safety outcomes were assessed in the intent-to-treat population. The study is complete (ClinicalTrials.gov NCT02504671).

Findings Between 23 July 2015 and 29 December 2017, 222 patients were randomised (n=37/group). At weeks 12 and 24, 86/175 (49·1%) and 57/83 (68·7%) escaped to otilimab 180 mg, respectively. At week 24, rates of DAS28(CRP) <2·6 were: 2/37 (5%), 6/37 (16%), 7/37 (19%), 5/37 (14%), and 5/37 (14%) in otilimab 22·5 mg, 45 mg, 90 mg, 135 mg, and 180 mg, respectively; 1/37 (3%) in the placebo group. The largest difference was achieved with otilimab 90 mg (16·2%; odds ratio [OR] 8·39; 95% confidence interval [CI] for OR 0·98, 72·14; p=0·0527). Across otilimab dose groups, AEs were reported pre-escape in 19–24 (51–65%) patients and post escape in 10–17 (40–61%) patients; in the placebo group this was 18/27 (27%) and 22/26 (50%), respectively. The most common AE was nasopharyngitis: pre-escape n=3–9 (8–24%) in otilimab groups, n=1 (1%) in the placebo group; post escape n=1–3 (4–10%) in otilimab groups, n=7 (21%) in the placebo group. Pre-escape SAEs were foot fracture (otilimab 45 mg); arthralgia, myocardial infarction, dizziness (otilimab 90 mg); oesophageal spasm, acute pyelonephritis (otilimab 22·5 mg), uterine leiomyoma (otilimab 135 mg), and dizziness. Post-escape SAEs were ankle fracture (placebo) and RA (otilimab 135 mg). There were no deaths or pulmonary events of clinical concern, and rates of serious infection were low.

Interpretation Otilimab plus methotrexate was well tolerated and despite not achieving the primary endpoint of DAS28(CRP) remission there were improvements compared with placebo in disease activity scores. Of particular note, patients reported significant improvement in pain and physical function, supporting further clinical development of otilimab in RA.

Funding GlaxoSmithKline.

Keywords: Anti-GM-CSF, CDAI, GSK3196165, DAS28(CRP), pain, patient-reported outcomes, rheumatoid arthritis

Research in context

Evidence before this study

We searched PubMed with the terms “rheumatoid arthritis” AND “mavrilimumab” OR “namilumab” OR “MOR103” OR “anti-GM-CSF” OR “anti-GMCSF”, with no restriction on language, for articles published between 2000 and 2015, i.e. prior to study start. We identified 4 clinical trials: one proof-of-concept Phase Ib/IIa trial of otilimab (MOR103) and 3 Phase I/II/IIa trials for mavrilimumab. Both agents showed evidence of efficacy for targeting granulocyte-macrophage colony-stimulating factor (GM-CSF) or its receptor in patients with rheumatoid arthritis (RA). Together with the strong preclinical evidence of a role for GM-CSF in the pathology of RA, and a need for alternative therapy options for RA, these findings supported the rationale to pursue the clinical development of otilimab, a monoclonal antibody that binds to and inhibits human GM-CSF. Furthermore, only one of the previous studies included assessment of patient-reported outcomes (PROs) beyond Health Assessment Questionnaire-Disability Index (HAQ-DI). In the Phase Ib/IIa otilimab study, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and pain Visual Analogue Scale (VAS) were also assessed; all PROs showed improvement following treatment with otilimab compared with placebo. The inclusion of a range of PROs in clinical studies is becoming increasingly important due to the chronic, long-term debilitating nature of the disease and ongoing disability for patients despite optimised clinical therapy. As such, a wider assessment of the impact of anti-GM-CSF treatment on PROs in RA was required.

Added value of this study

To our knowledge, this is the first clinical trial in the field of rheumatology with a novel study design offering an automated and blinded escape to a higher dose to patients with RA who had not obtained a meaningful benefit from their randomised treatment, with the aim to achieve an optimised ‘treat-to-target’ dosing regimen. We observed dose-related and meaningful clinical benefit with otilimab in patients with an inadequate response to methotrexate. Otilimab treatment led to rapid reduction in tender and swollen joint counts and hence Clinical Disease Activity Index scores. This is also (to our knowledge) the first clinical trial assessing an anti-GM-CSF antibody in RA to include a wide panel of PROs: HAQ-DI, pain VAS, short-form health survey and components, FACIT-Fatigue, Brief Fatigue Inventory – Question 3, and Patient’s Global Assessment of Arthritis Disease Activity. We observed substantial improvement in a range of these PRO measures, particularly in pain scores. Otilimab treatment was well tolerated and no significant unexpected safety findings were observed.

Implications of all the available evidence

The results of this study build on the existing data and support a positive benefit:risk profile of treatment with otilimab in active RA and provide a basis for further clinical development. Interestingly, the temporal changes in pain compared with the temporal changes in disease activity, including acute phase reactants (C-reactive protein), suggests a particular role for GM-CSF inhibition in pain response in active RA.

INTRODUCTION

Many patients with rheumatoid arthritis (RA) have an inadequate response to currently available disease-modifying therapies[1] with few achieving disease remission. Even when disease activity is reduced many patients continue to experience clinically significant pain, despite the availability of 'gold standard' treatments that suppress disease-associated inflammation and damage.[2] Thus, there is an impetus to investigate new treatments in RA that target pain as well as inflammation and damage, and explore whether disease activity, clinical remission, and pain are always associated or can be dissociated mechanistically and clinically.

In pathological conditions, granulocyte-macrophage colony-stimulating factor (GM-CSF)[3] is a key driver of inflammation, pain, and tissue damage in a range of immune-mediated disease states.[3-5] Levels of GM-CSF are elevated in the synovial tissue of some patients with RA[6,7] and GM-CSF augments myeloid cell activation,[8] leading to production of inflammatory cytokines such as interleukin (IL)-6, IL-1, tumour necrosis factor (TNF) and chemokine (c-c motif) ligand 17 (CCL17), which are associated with pain and can result in severe tissue damage.[3,9] Mechanistic studies indicate that GM-CSF is involved in the development of pain-like behaviour in mouse models of inflammatory pain and arthritis,[5,10] and a mouse sarcoma model demonstrated a role for GM-CSF in sensitising sensory nerves.[11] Therefore, anti-GM-CSF agents could have a key role in treating inflammation and pain in multiple conditions, including RA.[8,10]

Otilimab (also known as GSK3196165, MOR103, and MOR04357) is a high-affinity recombinant human monoclonal immunoglobulin G1 antibody that specifically binds to human GM-CSF, inhibiting its activity.[12] Phase I/II clinical trials in patients with RA indicated that inhibition of GM-CSF signalling by human monoclonal antibodies, including otilimab, leads to clinical benefit with a reduction in disease activity. [13-16]

This randomised, Phase IIb, double-blind, placebo-controlled, dose-ranging study assessed clinical responses, including inflammation and pain, across five doses of otilimab in combination with methotrexate (MTX) in patients with active, moderate-to-severe RA who had an inadequate response to MTX. The primary endpoint was the induction of disease remission. Other outcomes included suppression of inflammation and improvement in pain, in addition to other patient-reported outcome (PRO) measures recommended by American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR).[17,18] The trial design included an innovative feature of blinded escape to otilimab 180 mg based on the stringent criteria of good/moderate EULAR response at week 12, or on disease activity score for 28 joints with C-reactive protein (DAS[CRP]) >3·2 at week 24.

METHODS

Study design

This randomised, Phase IIb, dose-ranging, multicentre, double-blind, parallel-group, placebo-controlled study (**Appendix p7**) was conducted at 64 sites across 14 countries (**Appendix p 2**). This study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice and the ethical principles outlined in the Declaration of Helsinki.[19] Study ethical approval was obtained at all sites; the first ethical approval was obtained on 22 May 2015 for investigational sites in Canada (Schulman Associates Institutional Review Board, Inc). The full protocol is available on Clinicaltrials.gov: https://clinicaltrials.gov/ProvidedDocs/71/NCT02504671/Prot_000.pdf. Key protocol amendments are listed in **Appendix p2**.

Patients

Patients aged ≥18 years, with a clinical diagnosis of RA according to ACR/EULAR 2010 classification criteria,[20] receiving MTX and with a disease duration ≥12 weeks were eligible. All patients provided written informed consent.

Patients were required to have Functional Class I, II or III (1992 ACR Classification of Functional Status in RA,[21] swollen joint count in 66 joints (SJC66) ≥4, tender joint count in 68 joints (TJC68) ≥4 at screening and at day 1, DAS28(CRP) ≥3·2 at screening or DAS28 with erythrocyte sedimentation rate ≥3·2 at day 1. For pulmonary safety, patients were required to have diffusing capacity or transfer factor of the lung for carbon monoxide (D_{LCO}) ≥60% and forced expiratory volume in 1 second (FEV_1) ≥70% predicted at screening.

Patients with a history of other inflammatory rheumatologic or autoimmune disorders, clinically significant or unstable persistent cough or unexplained dyspnoea were excluded. See **Appendix p2–5** for full eligibility criteria.

Randomisation and masking

Patients were randomised (1:1:1:1:1:1) to six treatment groups: placebo or otilimab 22·5, 45, 90, 135 or 180 mg. Randomisation was blocked (block size six). Patients were assigned to treatment using central randomisation according to a schedule generated by the study sponsor using validated software. Randomisation numbers were assigned using an interactive response technology system. Randomisation was not stratified. Patient recruitment was performed by study investigators. To ensure blinding of treatment assignments during the study, an unblinded administrator (study co-ordinator or nurse) prepared and administered the study drug. Further information on blinding is provided in **Appendix p5**.

Procedures

Treatments were administered subcutaneously once weekly for the first 5 weeks, then every other week (EOW) from week 6 until week 50. The rationale for dose selection and guidelines for treatment withdrawal or interruption are provided in **Appendix p5–6**. A 12-week safety follow-up period began after the final dose. All patients continued to receive MTX 7·5–25 mg/week and folic (or folinic) acid ≥5 mg/week during the treatment period.

Patients not randomised to otilimab 180 mg escaped in an automated blinded procedure to otilimab 180 mg if they did not achieve a good/moderate EULAR response at week 12 or had DAS28(CRP) >3·2 at week 24. Any patients who did not achieve EULAR good/moderate response at week 36 were withdrawn from treatment at the next visit in an automated procedure.

Efficacy outcomes, Health Assessment Questionnaire-Disability Index (HAQ-DI) score, pain Visual Analogue Scale (VAS), and Patient's Global Assessment of Arthritis Disease Activity (PtGA) were assessed at screening, baseline (day 1), weeks 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, and at follow-up (week 62). Brief Fatigue Inventory – Question 3 (BFI-Q3), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, and 36-item short-form health survey (SF-36) were assessed at baseline, weeks 4, 12, 24, 36, and 52, and at follow-up. Blood samples for pharmacokinetic (PK) and biomarker outcomes were taken at baseline, weeks 1, 2, 4, 6, 8, 12, 24, 36, and 52, and at follow-up; additional blood samples for PK analysis only were taken at weeks 16 and 20.

Safety parameters were monitored throughout the study until follow-up, including monitoring of AEs, SAEs, AEs of special interest (AESI), infections, and immunogenicity. The following pulmonary assessments were performed at screening, day 1, week 12, 24, 36, and 52, and follow-up: chest X-ray at screening, cough, Borg dyspnoea questionnaire, lung auscultation, pulse oximetry throughout the study, spirometry (FEV_1, forced vital capacity), and D_{LCO}. Laboratory monitoring for haematology and chemistry was performed at screening, week 2,4, 8, 12, 16, 20, 24, 32, 42, and at follow-up; urinalysis was performed at the same time points, excluding week 2; cholesterol, triglycerides, and lipoproteins were assessed at screening, week 12, and 24, and follow-up.

Outcomes

The primary endpoint was the proportion of patients who achieved DAS28(CRP) remission (DAS28[CRP] <2·6) at week 24.

Secondary endpoints were: change from baseline (CFB) in DAS28(CRP) at week 12 and all other assessment time points; proportion of patients who achieved DAS28(CRP) remission at all time points; time to first DAS28(CRP) remission; ACR20/50/70 and good/moderate EULAR response rate at all time points; index- and Boolean-based ACR/EULAR remission rates, and CDAI remission rate at all time points; CFB in SJC66, TJC68, Simple Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI); CFB in PROs at all time points using HAQ-DI score, pain VAS, physical and mental component of SF-36, FACIT-Fatigue, and BFI-Q3. PK was assessed as a secondary objective; endpoints were: otilimab serum concentration and evaluation of the target engagement biomarkers free soluble GM-CSF and soluble GM-CSF complexed to otilimab (GM-CSF/otilimab complex).

Secondary safety endpoints were incidence of AEs and SAEs, infections, and pulmonary events. Any new or clinically significant pulmonary abnormalities (e.g. increased dyspnoea, unexplained and persistent coughing, or >15% relative decrease in D_{LCO} from baseline) were referred to a pulmonologist for further assessment in order to identify any cases of pulmonary alveolar proteinosis.

Statistical analysis

Based on a Fisher's exact test, a planned sample size of 35 patients per group provided ~90% power to detect a difference of 30% in the proportion of patients achieving DAS28(CRP) remission at week 24 between each otilimab dose and placebo at the 2-sided α=0·05 level (33% vs 3%). The difference of 30% between groups was based on the expected clinical profile for otilimab; the predicted placebo rate of 3% was based on the literature review of current therapies presenting DAS28(CRP) remission results. The efficacy and safety population was the intent-to-treat (ITT) population: all randomised patients who received ≥1 dose of study drug. The PK population was all randomised patients who received ≥1 dose of otilimab and had ≥1 quantifiable otilimab concentration available.

Binary endpoints, including the primary endpoint, were assessed using a logistic regression model adjusted for treatment group and appropriate baseline scores. A non-responder imputation was used for patients with missing efficacy data and those who escaped to otilimab 180 mg dose.

All continuous efficacy endpoints, including patient-reported outcomes such as VAS, HAQ-DI, SF-36, and FACIT-Fatigue, were analysed using mixed model repeated measures with fixed effects for treatment group and baseline value. CFB will be missing at visits with missing post-baseline values, and all patients who escaped to otilimab 180 mg were set to missing post escape. The serum otilimab and target engagement biomarker concentrations were summarised by descriptive statistics by treatment group and visit through week 52. A post hoc analysis was performed to evaluate the percentage of patients with pain improvement ≥minimal clinically important difference (MCID; 10 mm difference on 100 mm VAS).

Two interim analyses were planned. Interim 1 and 2 were conducted when 90 subjects completed week 4 and 12, respectively, to evaluate whether to terminate the study based on the dose response relationship in CFB in DAS28(CRP). Interim 2 also evaluated the predictive probabilities of observing a 25% difference at week 24 in DAS28(CRP) remission and the whether there was a need to terminate individual dose treatment arms. Following the interim analyses, the study was not stopped and there were no changes made to the treatment arms.

All analyses were conducted using SAS v9·3 (SAS Institute Inc., Cary, NC, USA). This study (BAROQUE, GSK study number 201755) is registered with ClinicalTrials.gov, NCT02504671. An independent data monitoring committee monitored the study.

Role of the funding source

This study (GSK study 201755; NCT02504671) was sponsored by GSK, which was involved in study design and conduct together with authors and investigators. Clinical data were collected by investigators and their teams, and GSK. All authors, including those employed by the funder, were involved in data analysis, interpretation of results and the preparation, review and approval of this manuscript. All authors had full access to all the data in the study, contributed to writing/reviewing of the report, and approved the final submitted version. The corresponding author had the final responsibility to submit for publication.

RESULTS

The study began on 23 July 2015 and completed on 29 December 2017. Of 526 patients with RA who were screened, 222 met the inclusion criteria and were randomised. A large proportion of patients escaped to the 180 mg dose at week 12 (**Figure 1**). No protocol violations impacted the interpretation of the study results (**Appendix p13**).

Baseline demographics, disease activity characteristics and PRO measures were balanced across treatment groups (**Table 1**), other than a higher proportion of female (180/222 [81%]) patients, which is typical for an RA population, and a slight imbalance in CRP, which was higher in the otilimab 22·5 mg group compared with other groups. Mean (standard deviation [SD]) age was 50·5 (11·27) years. Although the inclusion criteria allowed moderate-to-severe RA, baseline disease characteristics were indicative of severe RA: mean (SD) DAS28(CRP) was 6·19 (0·836) and mean (SD) disease duration ranged from 5·1 (6·4) years (45 mg group) to 7·7 (7·1) years (180 mg group). Mean (SD) CDAI was 44·31 (12·824). Mean (SD) pain VAS score was 67·0 (18·49); mean (SD) HAQ-DI score was 1·755 (0·556), and mean (SD) FACIT-Fatigue score was 25·7 (9·82).

At week 24, DAS28(CRP) <2·6 remission rates were consistently higher for all otilimab dose groups versus placebo, but none were statistically significant. The difference to placebo in DAS28(CRP) remission rate was 2·7–16·2%; the biggest difference was achieved with otilimab 90 mg (16·2%; odds ratio [OR] 8·39; 95% confidence interval [CI] for OR 0·98, 72·14; p=0·0527) (**Figure 2A**). The initial reduction in DAS28(CRP) was

rapid for all otilimab dose groups, followed by a slower rate of improvement from week 6 to 12. Based on the patients originally randomised to otilimab 180 mg, the improvement in DAS28(CRP) reached a plateau between weeks 12 and 24 (**Figure 2B**). A post hoc analysis indicated that, at week 24, the proportion of patients achieving DAS28(CRP) low disease activity (≤3·2) generally increased with increasing dose (**Appendix p14**).

There was a significant difference in DAS28(CRP) mean CFB between the 180 mg group and placebo at week 12 (−1·27 [95% CI −1·91, 0·63]; p=0·0001) and week 24 (−1·82 [95% CI −2·75, −0·89]; p=0·0002) (**Appendix p15–16**). Dose-response modelling for CFB in DAS28(CRP) at week 12 was conducted using a linear log-dose model; the model-predicted DAS28(CRP) response for otilimab 180 mg was −1·19 (95% CI −1·75, −0·63). Time to first DAS28(CRP) remission was shortest in the otilimab 90 mg dose group: mean (SD) 8·91 (4·022) weeks.

Given that a substantial number of patients had escaped to the 180 mg dose at week 12 and that target saturation was not achieved after week 8 (as described below), subsequent analyses included data up to and including the week 12 time point. Secondary endpoint data for all timepoints up to week 12 are provided in **Appendix p17–28**.

At week 12, significantly more patients receiving any otilimab dose achieved an ACR20 response versus placebo, and significantly greater response rates in ACR50 were achieved with the 45 mg and 135 mg doses versus placebo; there was no significant difference between placebo and otilimab groups for ACR70 response rate (**Figure 2C**). At week 12, good/moderate EULAR response rate was higher in the otilimab groups versus placebo. The highest proportion of patients with a good/moderate EULAR response was in the otilimab 180 mg group: 28/37 (76%); difference versus placebo 54·1% (95% CI 34·9, 73·2) OR 10·93 (95% CI 3·68, 32·51) p<0·0001. CDAI remission rate at week 12 was highest in the otilimab 90 mg dose group: difference versus placebo 8·1% (95% CI –3·2 to 19·7). Index- (SDAI ≤3·3) and Boolean-based ACR/EULAR remission rates could not be assessed due to low numbers of responders.

There was a rapid and substantial improvement in SJC66, TJC68, CDAI (**Appendix p8**) and SDAI in all otilimab dose groups versus placebo. For SJC66, there was a significant difference versus placebo in least squares (LS) mean CFB to week 12 in the 180 mg group (−7·54 [95% CI −11·78, −3·30; p=0·0006]) and the 90 mg group (−5·63 [95% CI −9·85, −1·41; p=0·0092]). For TJC68, the biggest difference versus placebo in LS mean CFB to week 12 was in the 180 mg group (−8·91 [95% CI –14·72, –3·10; p=0·0028]). The greatest change in CDAI from baseline at week 12 was observed in the otilimab 180 mg dose group, with a difference versus placebo of −16·63 (95% CI −23·97, −9·30; p<0·0001). For SDAI, the biggest difference versus placebo in LS mean CFB to week 12 was in the 180 mg group (–16·86 [95% CI –24·39, –9·32; p<0·0001). A sustained reduction in CRP levels from baseline to week 12 of ~50% was evident in otilimab dose groups of 45 mg and above, although these changes were not statistically significant versus placebo (**Appendix p8**).

Early, consistent and sustained (up to week 12) improvements from baseline were observed in all PRO measures (**Figure 3, Appendix p9–10**). By week 4 there was a significant difference in LS mean CFB in patient's assessment of pain (VAS) versus placebo for all doses of otilimab (except for the 22·5 mg and 135 mg doses). At week 12 there was a significant difference in pain versus placebo for all doses except for the 22·5 mg dose; the largest differences versus placebo were in the 90 mg dose group (−18·18 [95% CI −28·35, −8·01]; p=0·0005) and the 180 mg dose group (–17·94 [95% CI –28·18, –7·70]; p=0·0007) (**Figure 3A**). A post hoc analysis revealed that overall, otilimab treatment was associated with a higher proportion of patients with pain improvement ≥10 mm difference on 100 mm VAS (minimal clinically important difference; MCID) versus placebo, with the largest difference versus placebo in the 180 mg dose group at week 12 (46% [95% CI 22%, 69%]) (**Appendix p29**).

Although there were no statistically significant differences between otilimab dose groups and placebo in mean HAQ-DI scores at weeks 4 and 12, a MCID versus placebo was observed at week 12 in the 180 mg dose group (−0·24 [95% CI −0·49, 0·01; p=0·0585]) (**Figure 3B**). At week 12, treatment with otilimab was associated with significant improvements in PtGA in all dose groups from 45 mg and above versus placebo; the largest difference versus placebo was observed with the 90 mg dose (−17·40 [95% CI −27·44, −7·35]; p=0·0008) and the difference between 180 mg and placebo was −17·18 (95% CI −27·27, −7·10; p=0·0009) (**Figure 3C**). A dose-dependent decrease was observed in fatigue (FACIT-Fatigue) from week 4, reaching a statistically significant improvement at week 12 with the 180 mg dose (difference from placebo: 5·33 [95% CI 1·77, 8·89]; p=0·0035) (**Figure 3D**). There were statistically significant differences over placebo in BFI-Q3 with all doses from 45 mg at week 12. The largest difference from placebo in BFI-Q3 to week 12 was observed in the 180 mg dose group (95% CI −1·57 [−2·53, −0·62]; p=0·0013) (**Appendix p10**).

There was a dose-dependent improvement in SF-36 scores, observed in all SF-36 domains (general health, bodily pain, mental health, physical functioning, role emotional, role physical, social functioning, and vitality)

with all doses of otilimab at week 12 compared with placebo (except for the 22·5, 45, and 90 mg dose groups in the social functioning domain). For the otilimab 180 mg dose the difference versus placebo in SF-36 physical score was 4·11 (95% CI 1·22, 7·01; p=0·0056) at week 4 and 3·55 (95% CI 0·22, 6·88; p=0·0367) at week 12 (**Appendix p9**). Consistent with results from VAS assessment of pain, there was a significant improvement in SF-36 bodily pain scores at week 4 (otilimab 180 mg difference vs placebo: 5·08 [95% CI 2·14, 8·03; p=0·0008]); the improvement over placebo was observed up to week 12 for otilimab 180 mg, although statistical significance was not reached at this time point (difference vs placebo 3·43 [95% CI –0·13, 6·99; p=0·0586]). There were no notable differences observed in SF-36 mental score at week 4; however, improvements were observed at week 12 for all doses, but these did not reach statistical significance. The difference versus placebo for 180 mg dose was 0·10 (95% CI −4·01, 4·20; p=0·9636) at week 4 and 3·25 (95% CI −1·05, 7·54; p=0·1378) at week 12.

The mean serum concentration of otilimab increased in a dose-dependent manner and peaked at week 4; the decline in serum concentrations coincided with the transition to EOW dosing from week 6 (**Appendix p11**). In the 180 mg group, observed mean trough concentration was 713–936 ng/mL between week 8 and week 52 (**Appendix p12**). The otilimab trough concentrations were lower than predicted from historic PK data (GSK unpublished results). Consistent with PK observations, the concentration of GM-CSF/otilimab complex also increased in a dose-dependent manner, peaking at week 4, and then declined after the switch to EOW dosing after week 6 (**Appendix p11**). Separation between the 135 mg and 180 mg dose and overall decline was observed from week 8, suggesting the target was no longer saturated.

AE rates were balanced across all treatment groups and most AEs were mild or moderate (**Table 2**). No dose effect on AEs or other safety parameters were observed in the otilimab groups. The most common treatment-related AEs were nasopharyngitis, upper respiratory tract infection and anaemia pre-escape, and nasopharyngitis and upper respiratory tract infection post escape. The rates of cytopenia and serious infections were low and there was no significant incidence of anti-drug antibodies across treatment groups. There were no deaths, malignancies, or venous thromboembolism, nor any events of pulmonary toxicity of clinical concern. Changes in D_{LCO} were infrequent and small; persistent (≥15 days) D_{LCO} decrease from baseline >15% was observed in one patient in each otilimab treatment group (except 90 mg) pre-escape, and in six patients post escape (two patients in each of the groups originally randomised to placebo, 22·5 mg and 135 mg). These changes were not considered to be dose related or clinically significant. Persistent dyspnoea was experienced by one patient in the otilimab 90 mg group, pre-rescue, beginning on day 8; the patient showed no decrease in D_{LCO}, and no substantial change in FEV_1 and forced vital capacity between baseline and week 12. Pulmonary events led to treatment discontinuation in three patients. Mild pulmonary fibrosis was reported in one patient in the otilimab 22·5 mg group, which occurred post escape to 180 mg dose. One patient in the otilimab 180 mg group experienced mild persistent D_{LCO} decrease, which was associated with acute bronchitis. Mild persistent dyspnoea was reported in one patient in the placebo group after escape to otilimab 180 mg dose: no decrease in D_{LCO} was observed and a small (<5%) decrease in spirometry assessments was reported; the event was assessed as not related to study medication. None of the pulmonary events were assessed as pulmonary alveolar proteinosis.

Pre-escape, eight patients experienced nine AESIs: injection-site reactions, neutropaenia, serious infection, persistent dyspnoea, and persistent cough (**Appendix p30**). There were six post-escape AESIs reported by four patients during the study period: injection-site reactions and persistent dyspnoea (**Appendix p30**). There were no events of hypersensitivity reactions, opportunistic infections, or pulmonary alveolar proteinosis reported.

Six patients experienced SAEs pre-escape (foot fracture, arthralgia, myocardial infarction, oesophageal spasm, acute pyelonephritis, uterine leiomyoma, and dizziness; none were reported in the otilimab 180 mg or placebo groups) (**Appendix p31**). After escape to the 180 mg group, one event each of ankle fracture and RA were reported in the placebo and 135 mg groups, respectively. None of the SAEs (pre- or post-escape) were deemed to be related to study treatment.

DISCUSSION

In this Phase IIb dose-ranging study, the primary endpoint at week 24 was not achieved. Patients had severe RA at baseline, characterised by higher DAS28(CRP), pain and HAQ-DI levels compared with recent Phase IIb studies targeting GM-CSF.[16] Despite this high baseline disease severity, otilimab in combination with MTX demonstrated clinically meaningful efficacy over 12 weeks of treatment with a rapid reduction in DAS28(CRP) similar to other approved biologic agents,[22,23] and the treatment was well tolerated.

The primary endpoint of DAS28(CRP) remission was chosen based on its importance as a EULAR treatment goal in RA. Escape therapy ensured that only patients who obtained a meaningful benefit from their randomised

treatment would continue treatment at the randomised dose throughout the study.[24] This was based on the rationale that an optimised 'treat-to-target' dosing regimen may result in a higher proportion of patients achieving remission.[24] Indeed, the clinical benefit of frequent monitoring and treatment adjustments according to a prespecified target has been demonstrated in other randomised trials.[25]

Otilimab serum concentrations were lower than expected based on historic data from healthy volunteers (GSK data on file), resulting in suboptimal exposure during EOW dosing, from week 6 onwards. This discrepancy is likely due to the high apparent clearance of otilimab.[26] Consistent with this, levels of serum GM-CSF/otilimab complex showed that full target engagement was not achieved from week 6 onwards with EOW dosing. The findings confirm and extend those from a Phase IIa study (RENAISSANCE, GSK study 205180; ClinicalTrials.gov Identifier: NCT02799472), which assessed otilimab 180 mg compared with placebo in patients with RA receiving concomitant MTX over 12 weeks.[14]

Previous studies have shown that even among patients who achieve low disease activity, many still report significant pain that negatively affects their quality of life and may produce biologic, psychological, and social changes that could influence the future response to painful stimuli.[2,3,27] Consequently, pain is prioritised by patients with RA as a key unmet need.[2] Despite suboptimal pharmacological exposure with bi-weekly otilimab doses, and our study not reaching statistical significance for its primary endpoint of DAS28(CRP) <2·6 remission, there was a rapid, sustained, and consistent improvement in all PRO endpoints. In particular, the improvement in pain VAS score was significantly greater than placebo at doses ≥45 mg at weeks 8 and 12. Similarly, there were substantial improvements in other PRO measures, including function, disability, health-related quality of life, and fatigue. Of note, the 90 mg dose group had fewer patients who escaped to the 180 mg dose and trended towards better clinical outcomes compared with the 135 mg dose group. A slight imbalance in balance disease characteristics was also observed between these groups. Although this finding was investigated, no explanation was found. We may postulate that it could be an artefact of the small sample size or the baseline characteristics, but this is not confirmed.

The pathophysiology of RA is complex, and the biological basis of joint pain could in part be different from that of inflammation and bone damage.[2,5,10] Recent studies have shown that discrete subsets of synovial fibroblasts and macrophages that reside in distinct anatomical compartments of the joint are responsible for inflammation, tissue damage, and repair.[28,29] These observations have provided a cellular basis for the partial dissociation of inflammation and damage in RA and osteoarthritis. However, there has not been any formal exploration in a clinical study of the mechanisms by which disease activity, remission, and pain relate to each other in either RA or osteoarthritis. Traditional anti-TNF therapies reduce inflammation and halt bone destruction,[30] but may not target all the cell types associated with pain. GM-CSF plays a key role in the development of inflammatory and arthritic pain,[5] and inhibition of the GM-CSF→JMJD3→ IRF4→ CCL17 (granulocyte-macrophage colony-stimulating factor→jumonji domain-containing protein 3→interferon regulatory factor 4→chemokine [c-c motif] ligand 17) pathway ameliorates pain in osteoarthritis.[10] In the current study, while the improvement in pain was accompanied by decreased inflammation, as evidenced by reduced CRP (and SJC) at week 12, our findings suggest that the therapeutic response with otilimab is predominantly driven by improvements in clinical parameters, reflected by the large CDAI responses not influenced by CRP changes. Indeed, the beneficial effect of otilimab on pain continued to progress beyond CRP reduction. These findings raise the possibility that the impact of treatment on pain and inflammation may be partly dissociated in RA; further studies are required to explore this more fully.

One limitation was that the design resulted in a high percentage of escape from the placebo and the lower otilimab dose groups after week 12. As such, the nonsignificant difference versus placebo in DAS28(CRP) at week 24 should be interpreted with consideration of a large proportion of patients in the placebo group having received otilimab 180 mg. The high percentage of escape, together with lower than expected exposure of otilimab, is likely to have contributed to the relatively low patient numbers and remission rates at the primary endpoint, week 24. Despite this, the observed improvements in disease activity and the rapid reduction of associated pain over 12 weeks reflects important clinical benefits, especially for patients with long-standing active disease.[2] Phase III studies are underway to further establish the efficacy of otilimab in a larger population and over a longer period, using an optimised dose and regimen[26] (ClinicalTrials.gov Identifiers: NCT03980483, NCT03970837 and NCT04134728).

The study design allowed the safety of otilimab to be assessed over 50 weeks of treatment and 12 weeks of subsequent follow-up. No significant unexpected safety findings were observed. Otilimab was well tolerated, with low rates of cytopenia and serious infections, no significant incidence of anti-drug antibodies, no deaths and no pulmonary toxicity events of clinical concern (including pulmonary alveolar proteinosis), consistent with previous studies of otilimab and other antibodies targeting GM-CSF signalling.[13,14,16]

In conclusion, despite the suboptimal level of exposure with bi-weekly dosing from week 6, otilimab demonstrated significant reductions in RA disease activity at week 12, particularly on joint swelling and tenderness and PROs involving pain. The results of this study support further clinical development given the observed benefit:risk of inhibiting GM-CSF with otilimab in the treatment of active RA. Furthermore, they suggest that targeting GM-CSF may not only reduce disease activity but also markedly improve pain and function.

AUTHOR CONTRIBUTIONS

CDB, KD, ML, NM, JP, RW, and PPT contributed to the conception and design of the study.
CDB, JAS-C, and VZ contributed to the acquisition of data.
CDB, BB, KD, EF, AG, CH, DI, ML, JP, DS, RW, and PPT contributed to data analysis and/or interpretation.
All authors were involved in development of the manuscript and approved the final version.

DECLARATION OF INTERESTS

CDB has received consulting fees or other remuneration from GlaxoSmithKline (GSK); JAS-C, and VZ report no conflicts of interest; BB, KD, AG, CH, DI, ML, JP, and DS are employees and stockholders in GSK; EF, NM, RW, and PPT were employees and stockholders of GSK at the time of study conduct.

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DATA SHARING STATEMENT

Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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REFERENCES

1. Tak PP, Kalden JR. Advances in rheumatology: new targeted therapeutics. *Arthritis Res Ther* 2011; **13 Suppl 1**: S5.

2. Lee YC, Cui J, Lu B, et al. Pain persists in DAS28 rheumatoid arthritis remission but not in ACR/EULAR remission: a longitudinal observational study. *Arthritis Res Ther* 2011; **13**(3): R83.

3. Wicks IP, Roberts AW. Targeting GM-CSF in inflammatory diseases. *Nat Rev Rheumatol* 2016; **12**(1): 37–48.

4. Hamilton JA, Cook AD, Tak PP. Anti-colony-stimulating factor therapies for inflammatory and autoimmune diseases. *Nat Rev Drug Discov* 2016; **16**(1): 53–70.

5. Cook AD, Pobjoy J, Sarros S, et al. Granulocyte-macrophage colony-stimulating factor is a key mediator in inflammatory and arthritic pain. *Ann Rheum Dis* 2013; **72**(2): 265–70.

6. Hamilton JA, Piccoli DS, Cebon J, et al. Cytokine regulation of colony-stimulating factor (CSF) production in cultured human synovial fibroblasts. II. Similarities and differences in the control of interleukin-1 induction of granulocyte-macrophage CSF and granulocyte-CSF production. *Blood* 1992; **79**(6): 1413–9.

7. Xu WD, Firestein GS, Taetle R, Kaushansky K, Zvaifler NJ. Cytokines in chronic inflammatory arthritis. II. Granulocyte-macrophage colony-stimulating factor in rheumatoid synovial effusions. *J Clin Invest* 1989; **83**(3): 876–82.

8. Hamilton JA, Tak PP. The dynamics of macrophage lineage populations in inflammatory and autoimmune diseases. *Arthritis Rheum* 2009; **60**(5): 1210–21.

9. Achuthan A, Cook AD, Lee MC, et al. Granulocyte macrophage colony-stimulating factor induces CCL17 production via IRF4 to mediate inflammation. *J Clin Invest* 2016; **126**(9): 3453–66.

10. Conaghan PG, Cook AD, Hamilton JA, Tak PP. Therapeutic options for targeting inflammatory osteoarthritis pain. *Nat Rev Rheumatol* 2019; **15**(6): 355-63.

11. Schweizerhof M, Stosser S, Kurejova M, et al. Hematopoietic colony-stimulating factors mediate tumor-nerve interactions and bone cancer pain. *Nat Med* 2009; **15**(7): 802–7.

12. Eylenstein R, Weinfurtner D, Hartle S, et al. Molecular basis of in vitro affinity maturation and functional evolution of a neutralizing anti-human GM-CSF antibody. *MAbs* 2016; **8**(1): 176–86.

13. Behrens F, Tak PP, Ostergaard M, et al. MOR103, a human monoclonal antibody to granulocyte-macrophage colony-stimulating factor, in the treatment of patients with moderate rheumatoid arthritis: results of a phase Ib/IIa randomised, double-blind, placebo-controlled, dose-escalation trial. *Ann Rheum Dis* 2015; **74**(6): 1058–64.

14. Genovese MC, Berkowitz M, Conaghan PG, et al. A phase IIa mechanistic study of anti-GM-CSF (GSK3196165) with methotrexate treatment in patients with rheumatoid arthritis (RA) and an inadequate response to methotrexate. *Arthritis Rheum* 2018; **70 Suppl 9**: Abstract 2510.

15. Taylor PC, Saurigny D, Vencovsky J, et al. Efficacy and safety of namilumab, a human monoclonal antibody against granulocyte-macrophage colony-stimulating factor (GM-CSF) ligand in patients with rheumatoid arthritis (RA) with either an inadequate response to background methotrexate therapy or an inadequate response or intolerance to an anti-TNF (tumour necrosis factor) biologic therapy: a randomized, controlled trial. *Arthritis Res Ther* 2019; **21**(1): 101.

16. Crotti C, Biggioggero M, Becciolini A, Agape E, Favalli EG. Mavrilimumab: a unique insight and update on the current status in the treatment of rheumatoid arthritis. *Expert Opin Investig Drugs* 2019; **28**(7): 573-81.

17. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum* 1993; **36**(6): 729-40.

18. Castrejon I, Carmona L, Agrinier N, et al. The EULAR Outcome Measures Library: development and an example from a systematic review for systemic lupus erythematous instruments. *Clin Exp Rheumatol* 2015; **33**(6): 910-6.

19. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). 2016. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf (accessed 25 February 2019).

20. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; **62**(9): 2569–81.

21. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. *Arthritis Rheum* 1992; **35**(5): 498–502.

22. van de Putte LB, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004; **63**(5): 508–16.

23. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006; **54**(9): 2817–29.

24. van Vollenhoven RF, Nagy G, Tak PP. Early start and stop of biologics: has the time come? *BMC Med* 2014; **12**: 25.

25. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004; **364**(9430): 263–9.

26. Gupta A, Zecchin C, Watts S, Davy K, Layton M, Zamuner S. Model informed selection of Phase 3 dosing regimens not fully tested in Phase 2: anti-GMCSF mAb, GSK3196165 in moderate to severe rheumatoid arthritis. ACoP10; 2019; Orlando, Florida, USA; 2019.

27. Salaffi F, Di Carlo M, Carotti M, Sarzi-Puttini P. The effect of neuropathic pain symptoms on remission in patients with early rheumatoid arthritis. *Curr Rheumatol Rev* 2019; **15**(2): 154-61.

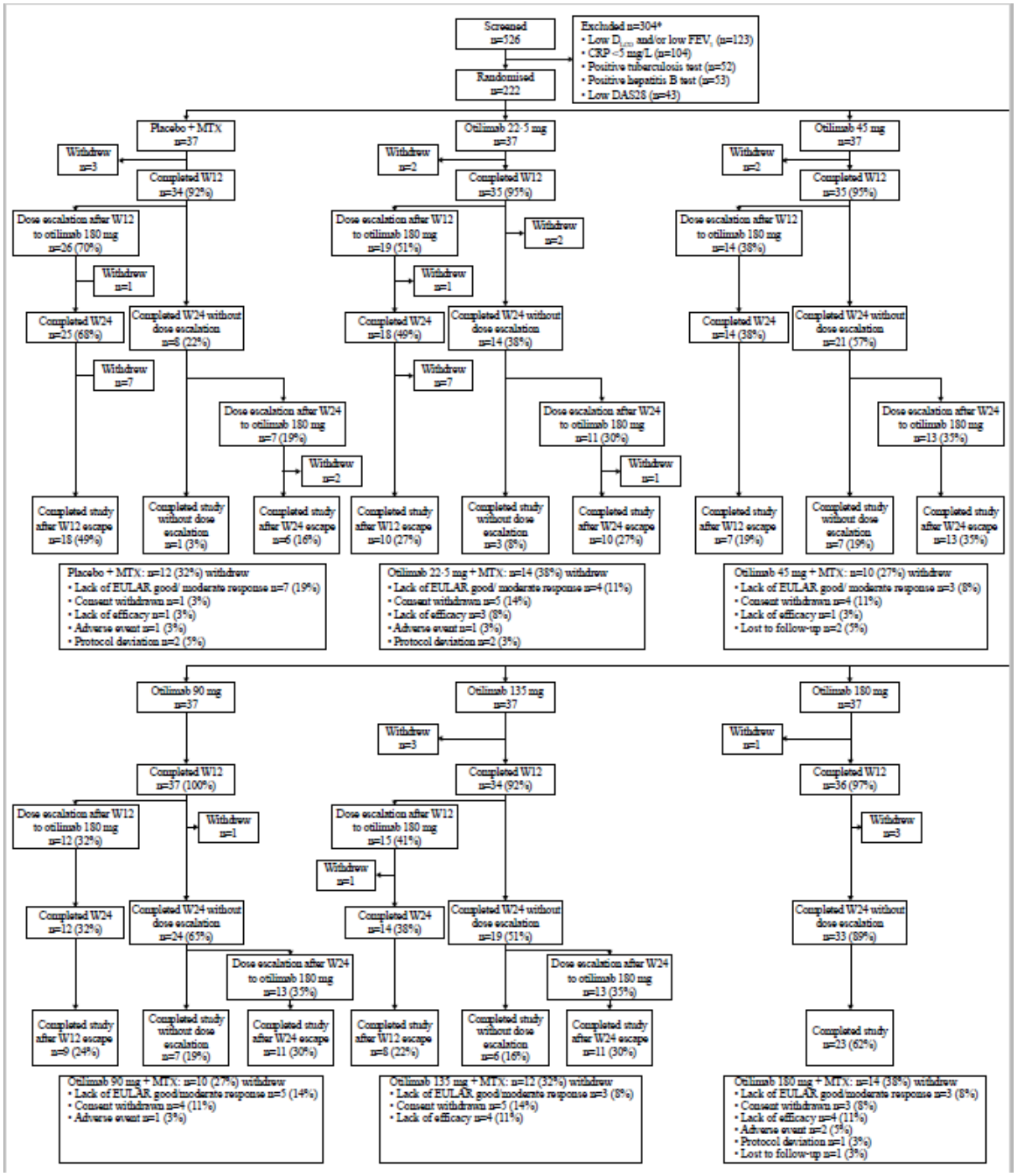
28. Croft AP, Campos J, Jansen K, et al. Distinct fibroblast subsets drive inflammation and damage in arthritis. *Nature* 2019; **570**(7760): 246-51.

29. Culemann S, Gruneboom A, Nicolas-Avila JA, et al. Locally renewing resident synovial macrophages provide a protective barrier for the joint. *Nature* 2019; **572**(7771): 670-5.

30. Taylor PC, Feldmann M. Anti-TNF biologic agents: still the therapy of choice for rheumatoid arthritis. *Nat Rev Rheumatol* 2009; **5**(10): 578–82.

FIGURES AND TABLES

Figure 1. Patient disposition.

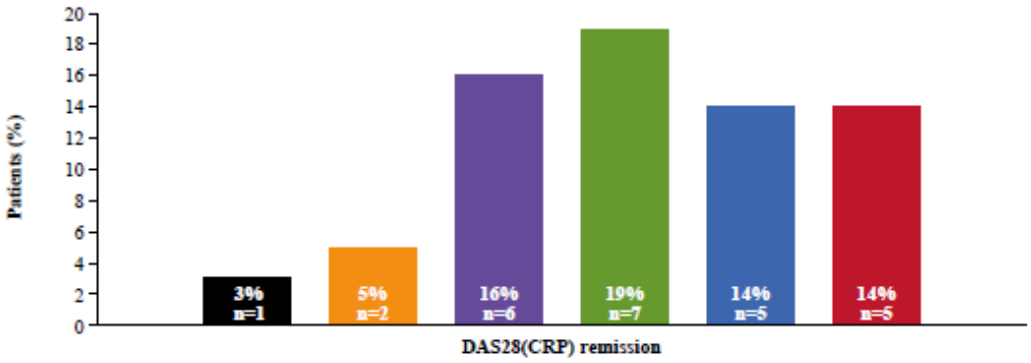


*Patients could be excluded for multiple reasons.

DAS28, Disease Activity Score for 28 different joints; D_{LCO}, diffusing capacity or transfer factor of the lung for carbon dioxide; EULAR, European League Against Rheumatism; FEV_1, forced expiratory volume in 1 second; MTX, methotrexate; n, number; W, week.

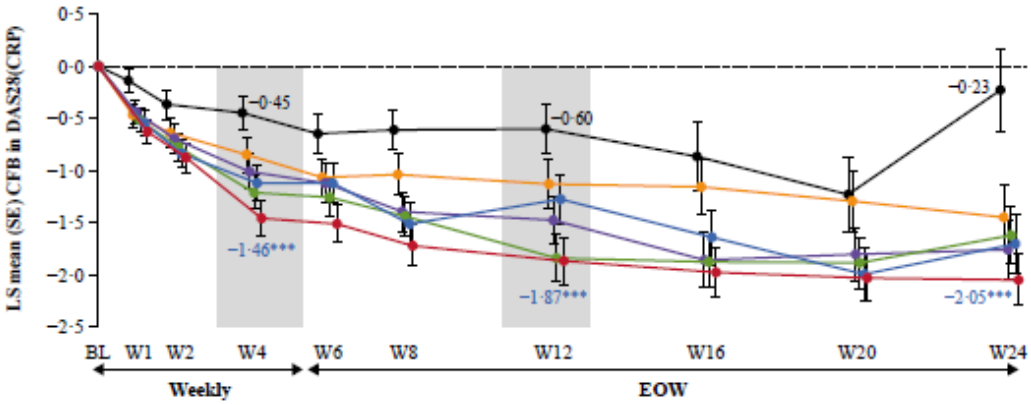
Figure 2. (A) DAS28(CRP) <2·6 remission rate at week 24 (B) DAS28(CRP) CFB over 24-week treatment period (observed results) and (C) ACR responses at week 12 (ITT population).

A.



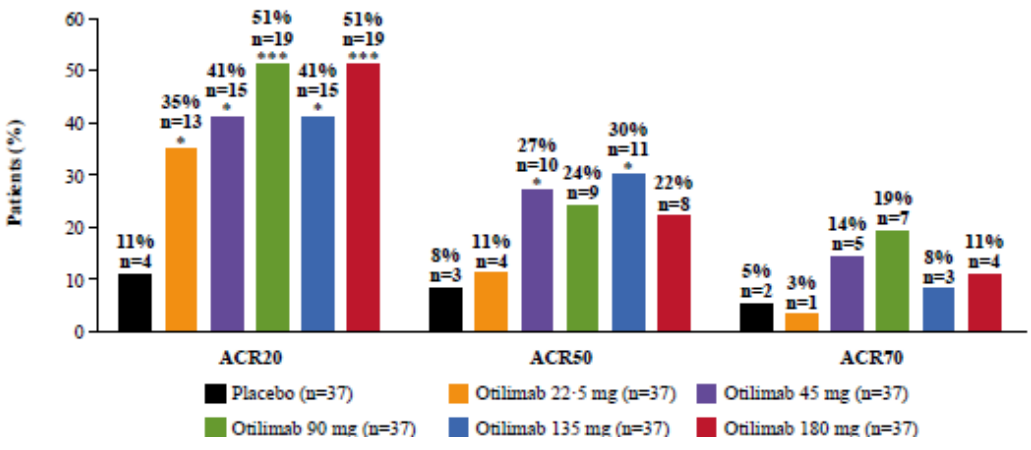
	Placebo (n=37)	Otilimab 22·5 mg (n=37)	Otilimab 45 mg (n=37)	Otilimab 90 mg (n=37)	Otilimab 135 mg (n=37)	Otilimab 180 mg (n=37)
Difference to placebo (%) (95% CI)	– –	2·7 (−6·3, 11·7)	13·5 (0·5, 26·5)	16·2 (2·6, 29·9)	10·8 (−1·4, 23·0)	10·8 (−1·4, 23·0)
Odds ratio (95% CI)	– –	2·12 (0·18, 24·52)	7·11 (0·81, 62·44)	8·39 (0·98, 72·14)	5·69 (0·63, 51·40)	5·40 (0·60, 48·83)
p-value	–	0·547	0·077	0·053	0·122	0·134

B.



Number of patients with non-missing data	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Placebo	32	34	34	8	8	8
Otilimab 22·5 mg	33	33	35	16	15	14
Otilimab 45 mg	34	34	33	20	20	20
Otilimab 90 mg	36	37	37	24	25	24
Otilimab 135 mg	36	35	34	18	19	19
Otilimab 180 mg	36	32	36	36	36	33

C.

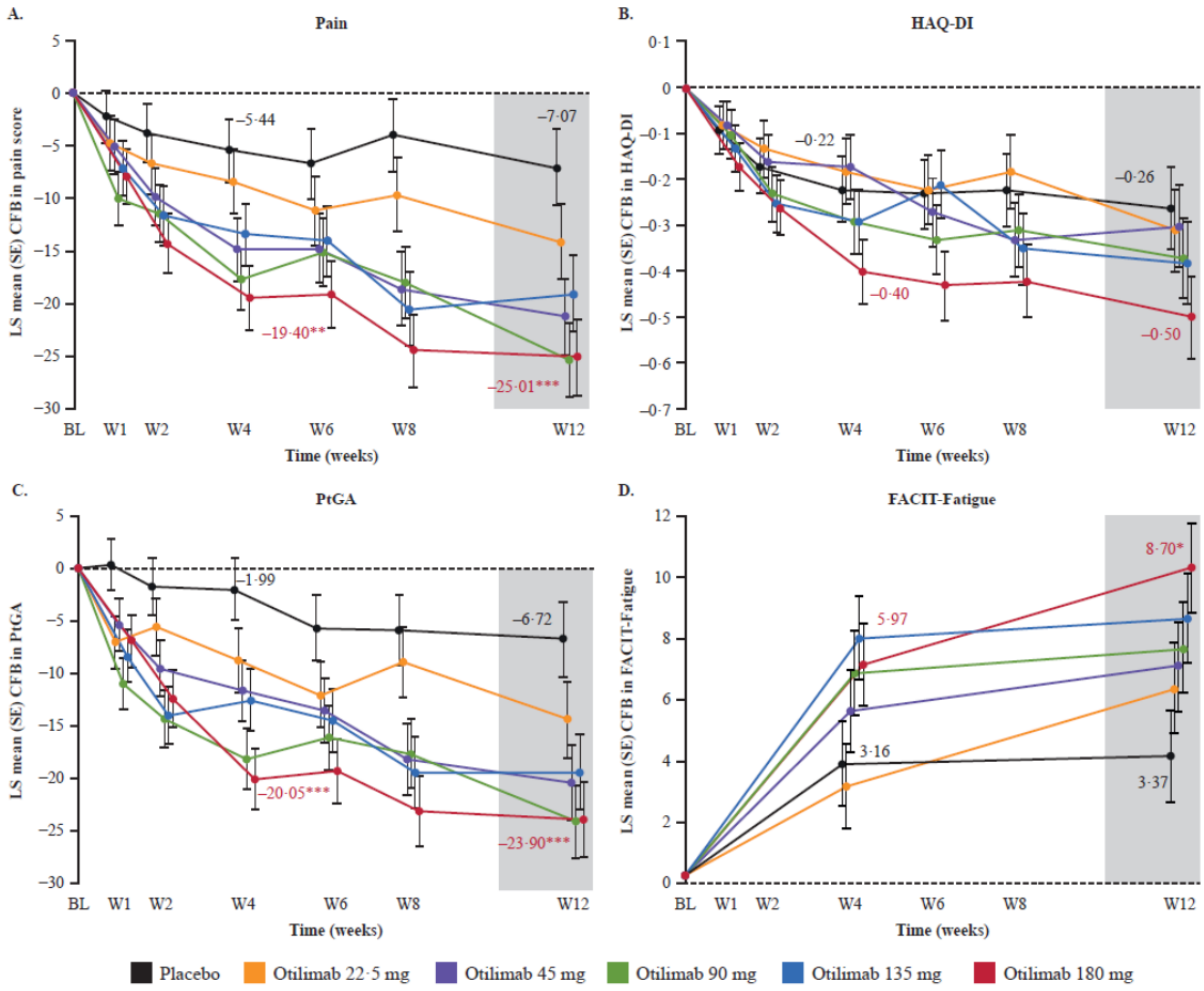


DAS28 (CRP) <2·6 remission rate at week 24 and ACR response at week 12 (binary endpoints) were analysed using logistic regression model by visit with fixed effects for treatment group and appropriate baseline score; non-responder imputation was used for patients with missing efficacy data and those who escaped to otilimab 180 mg dose.
DAS28 (CRP) CFB over the 24-week treatment period (continuous endpoint) was analysed using repeated measures analysis adjusted for DAS28(CRP) BL score, treatment group, visit and treatment group by visit, and BL by visit interactions. Patients who escaped to otilimab 180 mg at week 12 were set to missing. Data post-week 24 were excluded due to quantity of missing data. Values on graph are LS mean CFB at week 4, week 12, and week 24.

*p<0·05; **p<0·02; ***p<0·01; ****p<0·001 vs placebo.

ACR, American College of Rheumatology; BL, baseline; CFB, change from baseline; CI, confidence interval; CRP, C-reactive protein; D, day; DAS28, Disease Activity Score for 28 different joints; EOW, every other week; ITT, intent-to-treat; LS, least squares; SE, standard error; W, week.

Figure 3. LS mean CFB in (A) pain (B) HAQ-DI (C) PtGA (D) FACIT-Fatigue over time (ITT population).



*p<0·05; **p<0·01; ***p<0·001 vs placebo.
Repeated measures analysis adjusted for BL, treatment group, visit and treatment group by visit and BL by visit interactions.
Values on graph are LS mean CFB at W4 and W12. For FACIT-Fatigue higher scores indicate better quality of life. Pain and PtGA were assessed by VAS.
BL, baseline; CFB, change from baseline; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire-Disability Index; ITT, intent-to-treat; LS, least squares; PtGA, Patient's Global Assessment of Arthritis Disease Activity; SE, standard error; VAS, Visual Analogue Scale; W, week.

Table 1. Baseline patient demographics and clinical characteristics.

		Otilimab				
	Placebo (n=37)	**22·5 mg (n=37)**	**45 mg (n=37)**	**90 mg (n=37)**	**135 mg (n=37)**	**180 mg (n=37)**
Age (years), mean (SD)	50·0 (11·3)	48·4 (11·3)	52·8 (12·2)	52·7 (11·3)	47·1 (10·0)	52·3 (10·8)
Female, n (%)	28 (76)	30 (81)	33 (89)	27 (73)	33 (89)	29 (78)
RA diagnosis (years), mean (SD)	6·2 (7·9)	6·3 (6·8)	5·1 (6·4)	6·1 (6·0)	6·9 (5·6)	7·7 (7·1)
ACPA positive, n (%)	28 (76)	24 (65)	24 (65)	23 (62)	28 (76)	30 (81)
RF positive, n (%)	28 (76)	26 (70)	27 (73)	21 (57)	22 (59)	30 (81)
DAS28(CRP), mean (SD)	6·2 (0·8)	6·4 (0·8)	6·1 (0·7)	6·2 (0·8)	6·3 (0·9)	6·0 (0·9)
SDAI (0-86), mean (SD)	47·4 (13·3)	48·0 (12·9)	45·2 (12·0)	46·5 (13·0)	48·2 (14·6)	44·4 (14·0)
CDAI (0-76), mean (SD)	45·7 (13·5)	45·2 (11·8)	42·8 (12·1)	44·5 (12·6)	45·3 (13·5)	42·5 (13·9)
TJC68, mean (SD)	28·5 (13·6)	27·9 (12·1)	26·1 (14·1)	28·8 (14·8)	30·1 (14·8)	25·3 (12·4)
SJC66, mean (SD)	18·5 (9·3)	17·7 (8·5)	17·2 (8·9)	18·3 (10·1)	18·9 (10·2)	18·9 (10·1)
Pain (100 mm VAS), mean (SD)	66·1 (16·7)	71·2 (15·8)	70·1 (17·3)	65·8 (20·4)	67·1 (19·3)	61·6 (20·6)
PtGA (100 mm VAS), mean (SD)	66·0 (15·6)	72·5 (14·2)	71·6 (14·9)	68·2 (17·6)	69·6 (17·0)	63·2 (16·6)
PhGA (100 mm VAS), mean (SD)	64·2 (11·9)	67·5 (10·3)	67·1 (15·9)	65·9 (18·6)	67·2 (15·4)	64·1 (15·7)
FACIT-Fatigue, mean (SD)	24·7 (8·59)	25·9 (9·13)	26·5 (9·22)	25·1 (9·89)	24·3 (9·55)	27·6 (12·35)
BFI-Q3, mean (SD)	6·5 (1·91)	6·5 (2·17)	6·5 (2·04)	6·7 (2·08)	6·6 (1·91)	5·8 (2·51)
HAQ-DI, mean (SD)	1·77 (0·6)	1·72 (0·5)	1·88 (0·4)	1·3 (0·5)	1·80 (0·6)	1·63 (0·7)
SF-36 (Mental Score), mean (SD)	42·5 (9·4)	41·8 (9·9)	42·3 (9·4)	40·7 (10·4)	41·4 (12·6)	41·3 (13·1)
SF-36 (Physical Score), mean (SD)	29·0 (5·6)	28·6 (6·1)	28·6 (7·0)	30·2 (6·6)	28·5 (7·0)	31·8 (7·9)
hsCRP (mg/mL), median (range)	12·9 (2–66)	19·5 (3–135)	14·7 (1–158)	13·7 (1–99)	15·6 (1–261)	12·7 (2–103)
Prior DMARD medications, n (%)						
Methotrexate, methotrexate sodium	36 (97)	37 (100)	37 (100)	37 (100)	37 (100)	36 (97)
Sulfasalazine	5 (14)	6 (16)	3 (8)	8 (22)	9 (24)	6 (16)
Leflunomide	1 (3)	4 (11)	3 (8)	3 (8)	8 (22)	4 (11)
Hydroxychloroquine	2 (5)	2 (5)	4 (11)	1 (3)	3 (8)	2 (5)
Azathioprine	1 (3)	0	0	1 (3)	0	0
Chloroquine + chloroquine phosphate + chloroquine sulfate	2 (5)	2 (5)	0	1 (3)	3 (8)	1 (3)
Adalimumab	0	0	0	1 (3)	0	0
Oral glucocorticoids						
Oral glucocorticoid use, n (%)	15 (40)	24 (65)	20 (54)	22 (59)	21 (57)	22 (59)
Oral glucocorticoid dose (prednisolone equivalent, mg/day), mean (SD)	6·37 (2·1)	6·04 (2·9)	6·83 (2·6)	6·75 (3·0)	5·90 (3·2)	5·89 (2·7)

ACPA, Anti-cyclic citrullinated protein antibody; BFI-Q3, Brief Fatigue Inventory-Question 3; CDAI, Clinical Disease Activity Index; DAS28(CRP), disease activity score for 28 different joints with C-reactive protein value; DMARD, Disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high sensitivity CRP; PhGA, physician's global assessment of arthritis; PtGA, patient's global assessment of arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SDAI, Simplified Disease Activity Index; SJC66, swollen joint count for 66 different joints; TJC68, tender joint count for 68 different joints; VAS, Visual Analogue Scale.

Table 2. Adverse events (ITT population).

Pre-escape, n (%) [#]*		**Otilimab**				
	Placebo (n=37)	**22·5 mg (n=37)**	**45 mg (n=37)**	**90 mg (n=37)**	**135 mg (n=37)**	**180 mg (n=37)**
Any AEs	18 (49) [27]	19 (51) [36]	24 (65) [59]	22 (59) [54]	19 (51) [48]	24 (65) [64]
AEs leading to discontinuation of study medication	0	0	0	2 (5) [2]	0	2 (5) [2]
SAEs	0	2 (5) [2]	1 (3) [1]	2 (5) [3]	1 (3) [1]	0
Treatment-related AEs	2 (5) [2]	9 (24) [15]	6 (16) [13]	6 (16) [7]	5 (14) [7]	9 (24) [19]
Most common AEs†						
Nasopharyngitis	1 (3) [1]	3 (8) [3]	7 (19) [10]	3 (8) [3]	6 (16) [6]	9 (24) [12]
Upper respiratory tract infection	3 (8) [3]	2 (5) [2]	1 (3) [1]	2 (5) [2]	2 (5) [3]	3 (8) [4]
Anaemia	0	2 (5) [2]	1 (3) [1]	0	2 (5) [3]	5 (14) [5]
Alanine aminotransferase increase	0	1 (3) [1]	3 (8) [6]	2 (5) [2]	2 (5) [2]	0
Post- escape, n (%) [#]*	**Placebo (n=33)**	**22·5 mg (n=30)**	**45 mg (n=27)**	**90 mg (n=25)**	**135 mg (n=28)**	
Any AEs	22 (67) [50]	16 (53) [40]	11 (41) [47]	10 (40) [19]	17 (61) [38]	
AEs leading to discontinuation of study medication	1 (3) [1]	1 (3) [1]	0	0	0	
SAEs	1 (3) [1]	0	0	0	1 (4) [1]	
Treatment-related AEs	5 (15) [6]	6 (20) [16]	4 (15) [20]	0	6 (21) [12]	
Most common AEs†						
Nasopharyngitis	7 (21) [7]	3 (10) [3]	1 (4) [1]	2 (8) [3]	2 (7) [2]	
Upper respiratory tract infection	0	3 (10) [4]	2 (7) [2]	0	5 (18) [6]	
Anaemia	0	1 (3) [1]	0	0	2 (7) [2]	
Alanine aminotransferase increase	2 (6) [2]	0	2 (7) [2]	1 (4) [1]	1 (4) [2]	

*n=number of patients with ≥1 event; #=number of individual occurrences.
†AEs occurring in >5% of patients.
AE, adverse event; ITT, intent-to-treat; SAE, serious adverse event.